

Art Unit: 1656

This Office action is in response to Applicants' remarks received August 15, 2011.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 10, 16 are canceled. Claims 12-14 are withdrawn. Claims 1-9, 11, 15 are currently under examination.

Priority: The request for priority to EPO 03023637.6, filed October 16, 2003, is acknowledged. A certified copy of the foreign priority document has been filed in this case on April 13, 2006, and is in an English language.

Objections and Rejections

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 15 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 15 is drawn to a host cell, wherein it is a human cell. The claim does not expressly limit the host cell to an isolated human cell. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "isolated" in the claim would be remedial. See also 1077 O.G. 24, April 21, 1987.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1656

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 8-9, 11, 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites that in addition another spliceable nucleotide sequence which is inserted downstream of the promoter sequence and upstream of the modified factor VIII cDNA. It is unclear where upstream of the modified factor VIII cDNA is. Applicants should clarify if by upstream, the spliceable nucleotide sequence is upstream of the coding sequence of the modified factor VIII. Further clarification is requested.

Claim 15 is drawn to a host cell according to claim 11, wherein it is a human cell. Claim 15 is indefinite because claim 11 is drawn to a process claim.

Claims 2-4, 8-9, 11 are included in this rejection because they are dependent on claim 1 and fail to cure its defects.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 8-9, 11, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Negrier et al. (US 20030083257; previously cited) (Negrier '257) in view of Chan (EP 0874057; IDS 11.04.08).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131.

Negrier '257 disclose a modified factor VIII cDNA comprising at least one spliceable nucleotide sequence that is inserted into the wild-type factor VIII cDNA at the original position of at least one intron of the genomic factor VIII DNA, wherein said at least one intron is selected from the group consisting of intron 1 and intron 13 (p. 6 claims 1-2). Negrier '257 also disclose that a truncated FIX intron can be inserted in intron positions 1 and 13 (p. 2 [0025]). Negrier '257 disclose a linker peptide of at least two amino acids which are selected from lysine and arginine (p. 6 claim 11). Negrier '257 disclose an expression vector comprising the modified factor VIII cDNA and a host cell of animal origin comprising said expression vector (p. 6 claim 4-5). Negrier '257 also disclose a process for producing a recombinant human factor VIII protein (p. 6 claim 16). Negrier '257 do not teach an additional intron downstream of the promoter and upstream of the modified FVIII cDNA.

Chan discloses an improved vector comprising a cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor (abstract, p. 5 line 54). Chan further discloses that the vector comprises a coding sequence for Factor VIII located downstream

Art Unit: 1656

from the donor intron acceptor (p. 5 lines 56-57). Chan discloses that introducing said vector into a mammalian cell line increases Factor VIII expression (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the vector of Chan for the vector used in Negrier '257, wherein the vector comprises the modified factor VIII cDNA of Negrier '257 (claims 1-6, 8-9, 11, 15). The motivation to do so is given by Chan, which discloses that a vector comprising a Factor VIII cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor can increase Factor VIII expression.

Claim 8 is included in this rejection because Negrier '257 in view of Chan discloses the elements recited in claim 1; therefore, the modified factor VIII cDNA of Negrier '257 in view of Chan could reasonably be representative of the recombinant factor VIII recited in claim 8.

Reply: Negrier '257 has been withdrawn as an 102(a) and 102(e) reference and is now applied as a 103(a) reference. The deficiency of Negrier '257 to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

Claims 1-6, 8-9, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plantier et al. (2001 Thromb Haemost 86: 596-603; IDS 11.04.08, previously cited) in view of Chan (EP 0874057; IDS 11.04.08). Plantier et al. disclose a modified factor VIII cDNA where a truncated factor IX intron 1 sequence was inserted in place of factor VIII introns 1, 12, and 13

Art Unit: 1656

and also as a combination between introns 1 and 12, and introns 1 and 13 and expression vector comprising said modified factor VIII cDNA (p. 596, p. 597). Plantier et al. disclose that the factor IX splicing donor and acceptor sequences were placed just after or before the factor VIII coding sequence (p. 597, fig. 1). Plantier et al. further disclose a process for producing a recombinant factor VIII from said modified factor VIII cDNA and a host cell comprising said modified factor VIII cDNA (p. 598). Plantier et al. do not teach an additional intron downstream of the promoter and upstream of the modified FVIII cDNA.

Chan discloses an improved vector comprising a cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor (abstract, p. 5 line 54). Chan further discloses that the vector comprises a coding sequence for Factor VIII located downstream from the donor intron acceptor (p. 5 lines 56-57). Chan discloses that introducing said vector into a mammalian cell line increases Factor VIII expression (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the vector of Chan for the vector used in Plantier et al., wherein the vector comprises the modified factor VIII cDNA of Plantier et al. (claims 1-6, 8-9, 11). The motivation to do so is given by Chan, which discloses that a vector comprising a Factor VIII cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor can increase Factor VIII expression.

Art Unit: 1656

Claim 8 is included in this rejection because Plantier et al. in view of Chan discloses the elements recited in claim 1; therefore, the modified factor VIII cDNA of Plantier et al. in view of Chan could reasonably be representative of the recombinant factor VIII recited in claim 8.

Reply: Plantier et al. has been withdrawn as an 102(b) reference and is now applied as a 103(a) reference. The deficiency of Plantier et al. to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

Claims 1-6, 8-9, 11, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Negrier et al. (US 6271025; previously cited) (Negrier '025) in view of Chan (EP 0874057; IDS 11.04.08). Negrier '025 disclose a modified factor VIII cDNA wherein at least one insertion site of the truncated factor IX intron 1 is chosen from factor VIII intron 1 splice site, factor VIII intron 12 splice site, and factor VIII intron 13 splice site and a vector comprising said modified factor VIII cDNA (col. 15-16, see also Fig. 1). Negrier '025 also disclose a host cell comprising said vector comprising said modified factor VIII cDNA (col. 4 lines 37-61). Negrier '025 further disclose a HepG2 cell model comprising said modified factor VIII cDNA (col. 5 lines 15-33). Negrier '025 also disclose a process for producing a recombinant factor VIII protein (col. 5-6). Negrier '025 do not teach an additional intron downstream of the promoter and upstream of the modified FVIII cDNA.

Chan discloses an improved vector comprising a cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being

Art Unit: 1656

located between a second promoter and a donor intron acceptor (abstract, p. 5 line 54). Chan further discloses that the vector comprises a coding sequence for Factor VIII located downstream from the donor intron acceptor (p. 5 lines 56-57). Chan discloses that introducing said vector into a mammalian cell line increases Factor VIII expression (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the vector of Chan for the vector used in Negrier '025, wherein the vector comprises the modified factor VIII cDNA of Negrier '025 (claims 1-6, 8-9, 11, 15). The motivation to do so is given by Chan, which discloses that a vector comprising a Factor VIII cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor can increase Factor VIII expression.

Claim 8 is included in this rejection because Negrier '025 in view of Chan discloses the elements recited in claim 1; therefore, the modified factor VIII cDNA of Negrier '025 in view of Chan could reasonably be representative of the recombinant factor VIII recited in claim 8.

Reply: Negrier '025 has been withdrawn as an 102(b) reference and is now applied as a 103(a) reference. The deficiency of Negrier '025 to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

Art Unit: 1656

Claims 1-6, 8-9, 11, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Negrier et al. (US 6800461; previously cited) (Negrier '461) in view of Chan (EP 0874057; IDS 11.04.08).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Negrier '461 disclose a process for producing a recombinant factor VIII protein from a modified factor VIII cDNA (col. 17-18). Negrier '461 disclose a modified factor VIII cDNA wherein at least one insertion site of the truncated factor IX intron 1 is chosen from factor VIII intron 1 splice site, factor VIII intron 12 splice site, and factor VIII intron 13 splice site and a vector comprising said modified factor VIII cDNA (col. 3 lines 26-44, see also Fig. 1). Negrier '461 also disclose a host cell comprising said vector comprising said modified factor VIII cDNA (col. 4 lines 55-65). Negrier '461 further disclose a HepG2 cell model comprising said modified factor VIII cDNA (col. 5 lines 40-60). Negrier '461 do not teach an additional intron downstream of the promoter and upstream of the modified FVIII cDNA.

Chan discloses an improved vector comprising a cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor (abstract, p. 5 line 54). Chan further discloses that the vector comprises a coding sequence for Factor VIII located downstream

Art Unit: 1656

from the donor intron acceptor (p. 5 lines 56-57). Chan discloses that introducing said vector into a mammalian cell line increases Factor VIII expression (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the vector of Chan for the vector used in Negrier '461, wherein the vector comprises the modified factor VIII cDNA of Negrier '461 (claims 1-6, 8-9, 11, 15). The motivation to do so is given by Chan, which discloses that a vector comprising a Factor VIII cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor can increase Factor VIII expression.

Claim 8 is included in this rejection because Negrier '461 in view of Chan discloses the elements recited in claim 1; therefore, the modified factor VIII cDNA of Negrier '461 in view of Chan could reasonably be representative of the recombinant factor VIII recited in claim 8.

Reply: Negrier '461 has been withdrawn as an 102(e) reference and is now applied as a 103(a) reference. The deficiency of Negrier '461 to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

Claims 1-6, 8-9, 11, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Negrier et al. (US 6780614; previously cited) (Negrier '614) in view of Chan (EP 0874057; IDS 11.04.08).

Art Unit: 1656

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131.

Negrier '614 disclose a modified factor VIII cDNA wherein at least one insertion site of the truncated factor IX intron 1 is chosen from factor VIII intron 1 splice site and factor VIII intron 13 splice site and a vector comprising said modified factor VIII cDNA (col. 2 lines 9-18, col. 2 line 27). Negrier '614 also disclose Dami cells comprising said vector comprising said modified factor VIII cDNA (col. 5 lines 45-55). Negrier '614 also disclose a process for producing a recombinant factor VIII protein (col. 9-10). Negrier '614 do not disclose an additional intron downstream of the promoter and upstream of the modified FVIII cDNA.

Chan discloses an improved vector comprising a cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor (abstract, p. 5 line 54). Chan further discloses that the vector comprises a coding sequence for Factor VIII located downstream from the donor intron acceptor (p. 5 lines 56-57). Chan discloses that introducing said vector into a mammalian cell line increases Factor VIII expression (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the vector of Chan for the vector used in Negrier '614, wherein the vector comprises the modified factor VIII cDNA of Negrier '614 (claims 1-6, 8-9, 11, 15). The motivation to do

Art Unit: 1656

so is given by Chan, which discloses that a vector comprising a Factor VIII cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor can increase Factor VIII expression.

Claim 8 is included in this rejection because Negrier '614 in view of Chan discloses the elements recited in claim 1; therefore, the modified factor VIII cDNA of Negrier '614 in view of Chan could reasonably be representative of the recombinant factor VIII recited in claim 8.

Reply: Negrier '614 has been withdrawn as an 102(e) reference and is now applied as a 103(a) reference. The deficiency of Negrier '614 to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Negrier et al. (US 20030083257; previously cited) (Negrier '257) in view of Chan (EP 0874057; IDS 11.04.08). The teachings of Negrier '257 in view of Chan are outlined above. Negrier '257 disclose β -globin intron 1 (p. 6 claim 3); however, Negrier '257 do not teach β -globin intron 2.

Art Unit: 1656

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a β -globin intron 2 for the β -globin intron 1 because it would be reasonable for one of ordinary skill to substitute other introns of β -globin (i.e. β -globin intron 2) into the modified factor VIII cDNA since Negrier '257 discloses that β -globin intron 1 can be successfully inserted into a modified factor VIII cDNA (instant claim 7). Further, MPEP 2144.06 notes that substituting equivalents known for the same purpose is prima facie obvious.

Reply: As noted above, MPEP 2144.06 notes that substituting equivalents known for the same purpose is prima facie obvious. In this instance, it would be reasonable for one of ordinary skill to substitute other introns of β -globin (i.e. β -globin intron 2) into the modified factor VIII cDNA since Negrier '257 discloses that β -globin intron 1 can be successfully inserted into a modified factor VIII cDNA. Further, the deficiency of Negrier '257 to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Art Unit: 1656

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 11 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6800461 (Negrier '461) in view of Chan (EP 0874057; IDS 11.04.08). Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claim and the Negrier '461 claims are drawn to a process for the production of a factor VIII protein comprising preparing a modified Factor VIII cDNA wherein said Factor VIII cDNA is modified by insertion of a truncated factor IX intron in one or more splice sites of the factor VIII cDNA, introducing the modified factor VIII cDNA into a cell, and expressing the modified factor VIII cDNA in said cell to produce factor VIII protein. The Negrier '461 patent differs from the presently claimed invention by not reciting an additional intron downstream of the promoter and upstream of the modified FVIII cDNA.

Chan discloses an improved vector comprising a cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor (abstract, p. 5 line 54). Chan further discloses that the vector comprises a coding sequence for Factor VIII located downstream from the donor intron acceptor (p. 5 lines 56-57). Chan discloses that introducing said vector into a mammalian cell line increases Factor VIII expression (abstract).

Art Unit: 1656

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of the Negrier '461 claims by substituting the vector of Chan for the vector used in a method to express the modified factor VIII of the Negrier '461 claims because Chan discloses that a vector comprising a Factor VIII cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor can increase Factor VIII expression.

Reply: Firstly, it should be noted that the modification of the primary reference in light of the secondary reference is proper because the applied references are so related that the appearance of features shown in one would suggest the application of those features to the other. See *In re Rosen*, 673 F.2d 388, 213 USPQ 347 (CCPA 1982); *In re Carter*, 673 F.2d 1378, 213 USPQ 625 (CCPA 1982), and *In re Glavas*, 230 F.2d 447, 109 USPQ 50 (CCPA 1956). Further, it is noted that case law has held that one skilled in the art is charged with knowledge of the related art; therefore, the combination of old elements, herein, would have been well within the level of ordinary skill. See *In re Antle*, 444 F.2d 1168, 170 USPQ 285 (CCPA 1961) and *In re Nalbandian*, 661 F.2d 1214, 211 USPQ 782 (CCPA 1982).

In this instance, the deficiency of Negrier '461 to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

Claims 1-6, 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. US 6780614 (Negrier '614) in view of Chan (EP 0874057; IDS 11.04.08). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the Negrier '614 claims are drawn to a modified factor VIII cDNA comprising a factor IX intron inserted at intron position 1 and intron position 13 of the factor VIII cDNA and a process for producing a factor VIII from said modified factor VIII cDNA. The specification of Negrier '614 disclose intron positions 1 and intron positions 13 of factor VIII cDNA (col. 2 lines 9-18). The Negrier '614 patent differs from the presently claimed invention by not reciting an additional intron downstream of the promoter and upstream of the modified FVIII cDNA.

Chan discloses an improved vector comprising a cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream donor intron being located between a second promoter and a donor intron acceptor (abstract, p. 5 line 54). Chan further discloses that the vector comprises a coding sequence for Factor VIII located downstream from the donor intron acceptor (p. 5 lines 56-57). Chan discloses that introducing said vector into a mammalian cell line increases Factor VIII expression (abstract).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of the Negrier '614 claims by substituting the vector of Chan for the vector used in a method to express the modified factor VIII of the Negrier '614 claims because Chan discloses that a vector comprising a Factor VIII cDNA protein coding sequence, a first promoter and a downstream donor intron, the first promoter and downstream

Art Unit: 1656

donor intron being located between a second promoter and a donor intron acceptor can increase Factor VIII expression.

Reply: Firstly, it should be noted that the modification of the primary reference in light of the secondary reference is proper because the applied references are so related that the appearance of features shown in one would suggest the application of those features to the other. See *In re Rosen*, 673 F.2d 388, 213 USPQ 347 (CCPA 1982); *In re Carter*, 673 F.2d 1378, 213 USPQ 625 (CCPA 1982), and *In re Glavas*, 230 F.2d 447, 109 USPQ 50 (CCPA 1956). Further, it is noted that case law has held that one skilled in the art is charged with knowledge of the related art; therefore, the combination of old elements, herein, would have been well within the level of ordinary skill. See *In re Antle*, 444 F.2d 1168, 170 USPQ 285 (CCPA 1961) and *In re Nalbandian*, 661 F.2d 1214, 211 USPQ 782 (CCPA 1982).

In this instance, the deficiency of Negrier '614 to disclose or suggest an additional intron downstream the promoter and upstream of the modified FVIII cDNA is believed to be remedied by the Chan reference.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

Art Unit: 1656

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marsha Tsay/
Patent Examiner, Art Unit 1656

October 11, 2011